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Filed : **June 27, 2001**

REMARKS

Applicant thanks the Examiner for reviewing the instant application. Claims 1-62 and 84 are cancelled by this amendment. Claims 63-80 were previously cancelled in the preliminary amendment filed with the application. Claims 81-82, 85 and 88 are amended as set forth above. The specific changes to Claims 81 and 82 are shown using ~~strikethrough text for deletions~~ and underlined text for additions. New Claims 89-90 are added. Thus, upon entry of the above-listed amendments, Claims 81-83 and 85-89 are pending.

No new matter has been added by the new claims or by the amendments to Claims 81-82, 85 and 88. Claims 85 and 88 have been amended to correct claim formatting and generally for the cosmetics of the claims. Support for new Claims 89-90 is found throughout the specification and claims as filed, for example, in case studies 1-5 on pages 26-49 and in original Claim 85. Support for the amendment to Claim 81 is found throughout the specification, for example at page 12, lines 18-23; page 20, lines 16-23; and in original Claim 81. The amendment of Claim 82 is supported by the specification as filed, for example, at page 20, lines 21-22.

The discussion of the specific rejections set forth in the Office Action is provided below.

Discussion of Rejection under 35 U.S.C. § 112, 1st paragraph – Enablement

The Examiner rejected Claims 81-84 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner acknowledged that the specification was "enabling for compounds enhancing GABA-A neurotransmission (acamprosate) and for compounds capable of decreasing NMDA-type glutamate neurotransmission (magnesium N-acetylhomotaurinate, memantine, magnesium sulfate, magnesium oxide)."

Claim 81 has been amended as set forth above to recite "[a] composition comprising ... a first active moiety comprising acamprosate; and ... a second active moiety, comprising a NMDA-type glutamate-antagonist." As acknowledged by the Examiner, such compositions are enabled by the specification.

Therefore, Applicants submit that amended Claim 81 and the claims depending therefrom, are enabled. Reconsideration and withdrawal of the instant rejection is respectfully requested.

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Discussion of Rejection under 35 U.S.C. § 112, 2nd paragraph – Indefiniteness

The Examiner rejected Claim 82 under 35 U.S.C. § 112, second paragraph, as being indefinite. According to the Examiner, the term "compound" in Claim 82 is used in the claim to mean "a composition comprising at least two agents," while the accepted meaning is that a "compound" is a single agent.

Claim 82 has been amended to recite "wherein said first and second moieties are covalently linked." In view of the amendment of Claim 82, Applicants submit that the rejection is moot and request reconsideration and withdrawal of the rejection.

Discussion of Rejection under 35 U.S.C. § 102 – Anticipation

The Examiner has rejected Claims 81-84 under 35 U.S.C. § 102(b) as being anticipated by Olney (U.S. Patent No. 5,474,990). The Examiner argues that Olney anticipates because it teaches a composition comprising a GABA receptor agonist (barbiturate) and an NMDA antagonist (MK-801).

This rejection is moot because amended Claim 81 is limited to compositions that include acamprosate. Olney does not disclose a composition comprising acamprosate, and therefore it does not anticipate independent Claim 81 or any other claim.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 102.

Discussion of Rejection under 35 U.S.C. § 103 – Obviousness

The Examiner rejected Claims 85-88 under 35 U.S.C. § 103(a) as being unpatentable over Durlach (U.S. Patent No. 4,355,043) in view of Primes *et al.* (U.S. Patent No. 4,582,705).

The Examiner argues that Durlach teaches, among other things, acamprosate, but not in combination with an inorganic salt or a chelate of magnesium. The Examiner argues that Primes *et al.* teaches compositions and methods for alcohol detoxification. According to the Examiner, the methodology of Primes *et al.* includes a drug therapy that uses pentobarbital, and a nutritional therapy that includes magnesium replacement. The Examiner concludes that it would have been obvious at the time the invention was made to use Durlach's acamprosate compound with magnesium sulfate from Primes *et al.* The Examiner reasons that because the barbiturate used by Durlach, pentobarbital, is a GABA agonist, it would have been obvious to one of skill in the art to

use any other GABA agonist in the drug therapy part of the alcohol detoxification therapy of Primes *et al.* The Examiner argues that the requisite motivation to use Durlach's acamprosate instead of pentobarbital in the alcohol detoxification method is present because acamprosate has fewer side effects than pentobarbital.

Applicants respectfully disagree with the Examiner and argue that Claims 85-88 are not obvious over Durlach in view of Primes *et al.* for the reasons discussed below.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art must reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

First, even if the references are combined, they do not teach or suggest all of the claim limitations, and particularly each limitation of independent Claim 85 . Primes *et al.* does not disclose a composition that includes both the GABA agonist, pentobarbital, and magnesium. Even if acamprosate were substituted for the pentobarbital in the method of Primes *et al.*, the substitution still would not result in the formation of a composition with both acamprosate and magnesium. Primes *et al.* simply fails to disclose a composition with both agents. This is not surprising because it would be irrational to use a powerful barbiturate/sedative, such as pentobarbital, in a nutrient replacement composition.

In fact, one of skill in the art would not be motivated to combine a needed nutrient in a composition with a barbiturate such as pentobarbital, because the negative side effects and sedation associated with the barbiturate would render such a nutrient therapy impractical, dangerous, and generally unsatisfactory. To combine the agents in a composition would result in sedation of the patient whenever the nutrient was needed, and would expose the patient to the dangerous side effects of the barbiturate. Also, the awkward combination and use of a strong sedative would cause a low rate of compliance with the regimen. As a practical matter no one would incorporate a barbiturate – a highly controlled, potentially addicting substance – into a nutritional supplement preparation. Typically the latter are sold over the counter without a prescription. Primes describes a nutritional supplement and not the augmentation of a prescription drug with a mineral.

In sum, Primes *et al.* disclosed treatment regimens for acute and chronic alcoholism. The treatment regimen for chronic alcoholism included several different therapies. *See* Primes *et al.* at column 1, lines 52-54. The regimen included a drug therapy in which the powerful sedative pentobarbital is administered. *See* Primes *et al.* at column 1, lines 52-54. Another part of the regimen included a nutritional therapy, for example, magnesium replacement therapy for magnesium deficient alcoholics. However, Primes does not disclose a composition comprising both pentobarbital and magnesium. Therefore, if acamprosate were substituted for pentobarbital, there still would not be a composition with both acamprosate and magnesium based upon the disclosure of Primes *et al.* Thus, Primes *et al.* and Durlach, alone or in combination, fail to disclose each and every element of independent Claim 85.

Second, even if Primes does disclose a single composition with both agents, which it does not, there is no suggestion or motivation, found in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the references. The Examiner states that one of skill in the art would be motivated to substitute acamprosate for pentobarbital because both are GABA agonists. Applicants disagree. Such a motivation to interchange the agents is only found using impermissible hindsight based upon the instant application. Acamprosate is not interchangeable with pentobarbital. They are not structurally or pharmacologically similar. The agents are chemically different and acamprosate is not a barbiturate or a sedative. Acamprosate is so different from a barbiturate in its pharmacologic actions that no one would ever think of substituting one for the other. They do not bind to the post-synaptic membrane at the same site. Barbiturates cause tolerance and dependence; acamprosate does not. Also, acamprosate and pentobarbital are not used interchangeably in the treatment of alcoholism or any other condition. One of skill in the art would not be motivated to replace the powerful sedative, pentobarbital, with acamprosate. Only with the benefit of impermissible hindsight based upon Applicant's own invention is there a motivation to combine the two references.

Furthermore, Applicant submits that in this case secondary considerations such as unexpected results are relevant to the determination of non-obviousness. *See, for example, Graham v. John Deere, Co.*, 383 U.S. 1, 17 (1966). "Evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *See Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

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Here, secondary considerations, specifically unexpected results, are provided in the application. This objective evidence of unexpected results demonstrates that the instant claims are not obvious. As demonstrated by the case studies in the application, the combination of acamprosate and magnesium was unexpectedly synergistic and beneficial. For example, in case study 2 the administration of magnesium with acamprosate resulted in augmentation of the treatment of tardive dyskinesia. Likewise, in case study 3 the administration of magnesium with acamprosate resulted in even greater augmentation of the treatment of dyskinesia associated with Parkinson's disease. Similar augmentation and therapeutic enhancement was reported for case studies 4 and 5. Thus, the case studies provide objective evidence of non-obviousness because they demonstrate unexpected results from the combination of acamprosate with magnesium, specifically, augmentation or enhancement of the therapeutic benefit being studied.

For the above reasons, Applicant submits that Claims 85-88 are not obvious over Durlach in view of Primes. Reconsideration and withdrawal of the instant rejection under § 103 is respectfully requested.

Conclusion

Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. In light of the above amendments and remarks, the present application is believed to be in condition for allowance, and action to that effect is respectfully solicited. Applicant invites the Examiner to call the undersigned if any issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 7-25-2005

By: _____

Ned A. Israelsen
Registration No. 29,655
Attorney of Record
Customer No. 20,995
(619) 235-8550

1825075 072105